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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,467	05/25/2005	Colin Andrew Leach	P33030	9241

20462 7590 07/10/2008

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
07/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/510,467	LEACH ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13,16 and 17* is/are pending in the application.

4a) Of the above claim(s) *4 and 5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-11,13,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20041007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11, 13 and 16-17 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-3, 6-11, 13 and 16-17 drawn to compounds of formula (I) wherein X is N, corresponding process of preparation, composition and method of use) in the reply filed on March 25, 2008 is acknowledged.

Claims 4-5 and claims 1-3, 6-11, 13, 16 and 17 (**all in part**, drawn to compounds of formula (I) wherein X is CH) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on March 25, 2008.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of atherosclerosis, does not reasonably provide enablement for a method of treating a disease associated with activity of the enzyme Lp-PLA_2 generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The scope of the claims is not adequately enabled solely based on the activity related to Lp-PLA_2 inhibition provided in the specification. First, the instant claims cover disorders that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test procedure and assay are provided in the specification in pages 29-30 and it was concluded that 'the compounds of the invention had IC_{50} values in the range of <0.1 to 100nM', however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the prevention of all types of primary and secondary acute coronary events embraced by the instant claims.

The specification provides that the compounds of the invention have therapeutic activity related to numerous diseases (see page 7, lines 22-29):

> The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA_2 and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid oxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, ischaemia, reperfusion injury, sepsis, and acute and chronic inflammation.

Some of the above disease have been proven to be extremely difficult to treat. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

A state of the art reference, Iribarren et al. (Arterioscler Thromb Vasc Biol. 2005) regarding Lp-PLA_2 activity, indicates that "Additional studies are warranted to elucidate the contributions of Lp-PLA_2 bioproducts on the risk of atherothrombosis and the value of selective inhibitors of Lp-PLA_2 activity in combating atherosclerosis" (see page 220). Not one compound -- let alone a genus of trillions of compounds, could possibly be effective against all of the disorders listed in the specification.

Endothelial dysfunction is a physiological dysfunction of normal biochemical processes carried out by endothelial cell, the cells that line the inner surface of all blood vessels, arteries and veins. Compromise of normal function of endothelial cells is characteristic of endothelial dysfunction. Normal functions of endothelial cells include mediation of coagulation, platelet adhesion, immune function, control of volume and electrolyte content of the intravascular and extravascular spaces. Endothelial dysfunction can result from disease processes, as occurs in septic shock, as well as from environmental factors, such as from smoking tobacco products. A state of the art reference, Lerman (2002) provides that – "Although various interventions were shown to be associated with improvement of endothelial function, little is currently known about the clinical and prognostic impact of therapeutic improvement of endothelial function" (see http://www.nhlbi.nih.gov/meetings/workshops/wise/session02_lerman.pdf). Another reference,

Koren (2002) indicates that "There are no specific published guidelines for the treatment of left ventricular diastolic dysfunction" (see http://www.dcmsonline.org/jax-medicine/2002journals/Feb2002/diastolic.htm).

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims are seen to encompass methods for treating as well as

preventing diseases associated with acute coronary events, which include atherosclerosis, diabetes, stroke, etc. (as per specification page 2, lines 6-8).

The nature of the invention

Currently, there are no known agents with the chemotherapeutic efficacy to treat all types of diseases associated with activity of the enzyme Lp-PLA_2. The art does not disclose an active agent or combination of active agents, which are recognized to treat the conditions cited supra. The prior art does not teach or disclose a treatment modality wherein healthy subjects are administered an active agent or agent(s) and there is evidence that none of the associated symptoms or disease state characteristics are ever manifested. The disclosure does not direct the skilled artisan to art, which satisfies the requirement for treating all types of diseases based on the Lp-PLA_2 inhibition activity.

The state of the prior art

There was no conclusive evidence for the treatment of **all** of the diseases encompassed by the claim with a single therapeutic agent in the state of the art.

The level of one of ordinary skill

The level of skill is that of a MD or PhD.

The level of predictability in the art

Since the art does not disclose any chemotherapeutic preventive agents, the skilled artisan would not predict, in the absence of proof to the contrary, that the active agent(s) instantly claimed compounds are efficacious in treating diseases such as endothelial dysfunction, etc. The assertion of a broad application as set forth in the instant method claims necessarily requires evidence to support applicant's asserted methods. The examiner notes there are no known

pharmaceutical agents recognized as therapeutic agents for the conditions claimed, and one of skill in this art could not predict, from the evidence of record, that the active agents asserted to be useful in the instantly claimed method, can indeed treat all types of diseases associated with the enzyme Lp-PLA_2.

The amount of direction provided by the inventor

The examiner notes, there is not seen sufficient guidance provided in the form of administration profiles, combination ratios of the active agents or references to same in the prior art to provide the skilled artisan with sufficient guidance to practice the instant therapeutic method.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). There is not seen in the disclosure, sufficient evidence to support applicant's claims of prevention. There is not seen sufficient working examples or data from references of the prior art providing a nexus between that which applicant asserts as proof of a method for treating all types of diseases associated with the enzyme Lp-PLA_2 or extrapolation from the data and evidence currently provided on the record to support methods drawn to treating such conditions.

The quantity of experimentation needed to make or use the invention

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and

complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment of the claimed disorders nor indicate competent technical references in the appropriate method of treating.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6-11, 13 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In claim 1, it is recited that "A compound.... **and** a pharmaceutically acceptable salt thereof", which is unclear because it is not clear if 'a compound or a salt thereof' is

claimed **or** 'a **mixture** of a compound and the salt' is claimed. Replacing with -- A compound…… ~~and~~ or a pharmaceutically acceptable salt thereof -- would overcome the rejection.

2. In claim 1, in the definition of R^4, and further the term "Het" is defined as "heterocyclyl ring **comprising** N and ….' (two occurrences). In this recitation, the term "comprising" is open ended. 'Comprising' in a compound claim, leaves the claim open for the inclusion of unspecified heteroatoms. The use of the above phrase causes the claim to be broader than the invention. See *In re Fenton*, 451 F.2d 640, 171 USPQ 693 (CCPA 1971). The discrepancy is also observed in claim 8. Replacing the recitation with -- heterocyclyl ring ~~comprising~~ having N -- is suggested (in all occurrences).
3. Claim 17 is an independent claim, however, the claim does not contain the structural formula (I) or the definitions of the variables. The claim recites ".... are as hereinbefore defined", however, the claim does not refer to any other claim. A claim to be independent must contain all limitations within the claim or should be written as a dependent claim which contains the necessary limitations. (***Note***: The claim as presented in the preliminary amendment filed October 7, 2004 did not contain a status identifier of "original").

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-3, 6-11, 13, 16 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Hickey et al., WO 01/60805. The instant claims read on the reference disclosed compounds, see the structural formula (I) in page 2, the corresponding species of Examples 67, 73, 80, 81, etc. and the process of preparation in pages 9-11. The compounds are disclosed to be useful as therapeutic agents, see page 7.

2. Claims 1-3, 6-11, 13 and 16-17 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 02/30911 (International filing date: October 5, 2001). The instant claims read on reference disclosed compounds, see formula (I) in page 2 and the corresponding compounds of Examples 7-11, 81, 88-98, etc.

The applied reference has a common inventor/assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-3, 6-11, 13 and 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over pending claims of each of copending Applications No. 11/871,178; 11/626,875; 11/626,879; 11/626,882; and 11/456,129 (now allowed). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in each of the application. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the

genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 1-3, 6-11, 13 and 16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,153,861. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims substantially overlap the compounds of the reference claims, see the claims in the issued patent. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the compounds from the reference claims and/or use the compounds in any of the methods taught by the reference, including those instantly claimed, because the skilled artisan would have had the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as pharmaceutical therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Receipt is acknowledged of the Information Disclosure Statement filed on October 7, 2004 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

July 9, 2008